THE EFFICACY OF COMPLEMENTARY AND ALTERNATIVE MEDICINE METHODS FOR CHRONIC EPILEPSY IN PEDIATRIC PATIENTS A PRISMA SYSTEMATIC REVIEW AND META-ANALYSIS

by

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ABSTRACT

Determining the efficacy of Complementary and Alternative Medicine (CAM) methods for the benefit of clinically diagnosed epileptic patients (ICD-10 code G40, definition found in Appendix) is imperative for developing funding strategies that support these methods, as well as for the success of promoting and improving education about these methods to achieve a truly multidisciplinary field of medicine. Additionally, CAM methods (i.e., ketogenic diets, comprehensive neurobehavior treatment (CNB), yoga, Ayurveda, botanicals, and electroencephalogram (EEG) biofeedback) benefit neurologic patients, the profession, practitioners, researchers, policy makers, and the public at large.[1] Even with controlled seizures, epilepsy can present a host of issues that can hinder a child's development and ability to function normally. Cognitive, behavioral, social, emotional, and other functionalities/abilities critical to normal development are all affected. There is limited research demonstrating efficacy of CAM therapies alone or coupled with that of an antiepileptic drug (AED). Further, it is unclear how consistent use of CAM therapies may impact the overall therapeutic success in pediatric epilepsy in the near future.

Dozens of scientific publications exist on CAM methods and the overall impact on epilepsy. However, most of these studies were conducted in the past century and outside of North America, focused on adult patients, and included too few subjects to establish efficacy. With guidance from Covidence, this meta analysis reviewed seven of forty available publications that met the inclusion criteria for pediatric epileptic patients under the age of 25 years old who

[1] NIH. *Complementary and Alternative Medicine (CAM).* 2020

were treated with CAM therapies and monitored over a 12 month span within the United States between the years 2000 – 2021.

All seven studies reported the use of CAM therapies such as keto diets, homeopathy / osteopathy, and comprehensive neurobehavioral treatment. The analysis of those studies revealed a statistically significant reduction in seizures for epileptic children utilizing CAM therapies ($p = .0062$ and $p = .0059$). The sample size of subjects was determined by article selection. A total of 671 subjects, calculated from the 7 selected studies, were considered for evaluation. Of these, 388 were excluded as they did not fit criteria for age and seizure duration or discontinued the use of CAM therapy. This exclusion resulted in a remainder of 283 subject participants. All subjects reported ≥ 50% reduction in seizure occurrence per month. Furthermore, 137 subjects (48%) reported complete seizure control. However, limited study size, small population, and a lack of long-term follow-up of treatment for pediatric epilepsy indicate the need for further research and therefore call for additional funding.

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1. Introduction

Epilepsy, the most common neurological disorder known to pediatricians and pediatric neurologists, affects 1% of children, and can have many adverse effects after its initial diagnosis. Epilepsy is primarily characterized by the tendency of unprovoked and reoccurring seizures that have no known etiology. Approximately 50 million people worldwide have been diagnosed with epilepsy, a chronic noncommunicable disease of the brain.[2] Epileptic episodes can vary in severity and frequency, ranging from muscle spasms to prolonged convulsions that may present less than once per year to several times a day.

The incidence of epileptic episodes is estimated to be five to eight new cases per 1000 population by the age of 11, with nearly 50% of all epilepsy beginning under the age of 16 years.[3] The highest frequency of epileptic episodes occur within childhood, the period of life pragmatically defined as 14-18 years of age, and in the adulthood 30-65 years of age. When assessing an adolescent or adult with epileptic symptoms, an accurate diagnosis is critical as life-changing consequences including cognitive impairment, declined neurologic functionality, neurotoxic adverse effects, and increased behavioral side effects, may result from an erroneous diagnosis[4][5].

As the cases of misdiagnosis of epilepsy occur with paroxysmal disorders, disorders in which symptoms develop abruptly and result in physical dysfunction, it is critical to understand

[2] World Health Organization. *Epilepsy*. 2019
[3] Panebianco et. al., *Yoga for Epilepsy.* Issue 10 & Appleton. *Treatment of Childhood Epilepsy*. 419-431
[4] Zupec-Kania & Spellman. *An Overview of The Ketogenic Diet for Pediatric Epilepsy*. 589-96
[5] Appleton, *Epilepsy in the Teenager.* 232-235

the disease difference of epilepsy in early childhood and epilepsy during adulthood. These differences are not only academic of value, they can also aid in diagnosis, treatment, and prognosis. R.E. Appleton outlines some vital differences between both age groups (Table 1).[6]

Table 1. *Differences Between Childhood and Adult Epilepsy*

1. Large differential diagnosis
2. Heterogeneous condition
    a. Many epilepsy syndromes
    b. Many causes
    c. Many prognoses
3. Most cases are idiopathic
4. Not a static condition; evolves with age
5. Not necessarily a chronic condition
6. Unclear relationship between seizures and cognitive/behavioral difficulties
7. Treatment must take account of educational issues and family dynamics
8. Consideration of the adverse effects from AEDs on the immature, developing brain

Patients clinically diagnosed with epilepsy have multiple treatment options available to them, including antiepileptic drugs (AED), surgery, and complementary and alternative medicine (CAM) therapies. CAM therapies are defined by both the National Center for Complementary and Alternative Medicine (NCCAM) of the National Institutes of Health (NIH) and the National Center for Complementary and Integrative Health (NCCIH) of NIH as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine".[7] NCCIH refers to the concepts of "alternative" and "complementary" differently:[8]

- "If a non-mainstream practice is used **together with** conventional medicine, it's considered "complementary.
- If a non-mainstream practice is used **in place of** conventional medicine, it's considered "alternative."

[6] Appleton, *Treatment of Childhood Epilepsy. 419-431*
[7] Tabish, S. *Complementary and Alternative Healthcare: Is it Evidence-based?* V-IX
[8] NCCIH. *Complementary, Alternative, or Integrative Health: What's In a Name?* 2018

With these definitions provided by the NCCIH, an appreciation of both the strengths and limitations of conventional medicine is necessary for the imminent development of conceptual integration models that can guide both public and private decision-making surrounding CAM research funding, research and practice.

From their introduction in 1857, nearly 200 years ago, AED's have shown their efficacy in the treatment of epilepsy. This has resulted in the identification and development of several iterations of AEDs. AEDs currently in use have improved tolerability and increased treatment options compared to previous formulations. Conventional medicine practitioners have dedicated decades to the development of allopathic treatments and research for neurological disorders such as AEDs, EEG, MRI, PET scans, vagus nerve stimulators, and brain surgery. However, not only can patients that present with similar symptoms experience a diverse set of reactions to or benefits from AEDs, but there is an absence of treatments that prevents the onset of epilepsy. Present-day researchers and clinicians have come to realize that to yield new pharmacological treatments in epilepsy, they must target therapies for specific subpopulations with drug-resistant epilepsy.[9]

The broad variety of CAM therapies that are available can be categorized within eight subsidiary categories of complementary and alternative medicine. Nicole Hartmann et. al., list them as homeopathy, osteopathy, acupuncture, electroencephalography (EEG) biofeedback, naturopathic treatment, yoga, kinesiology, vitamins, and herbal remedies[reference]. Of the listed therapies,

[9] Privitera M. *Epilepsy Treatment: A Futurist View*. 2017

only three- ketogenic diet, immunoglobulins, and steroids- play substantial roles in the treatment of intractable childhood epilepsy due to having been studied more extensively. However, their impact on therapeutic success of seizure frequency reduction has not been adequately studied or documented. Despite the lack of scientific rigor in understanding their efficacy, mechanism of action, and safety, the three therapies introduced above have been partially accepted within medical doctrine. Until critical evaluation of alternative therapies is conducted, the medical community will continue to reject the implementation of alternative treatments. So far, studies on the use of the above-mentioned therapies have either: 1. *Demonstrated clear efficacy and result in patients with an unclear mechanism of action, or 2. Displayed both unknown efficacy and mechanism of action*.[10,11,12,13,14] The intent of this analysis is to review the effect of CAM therapies on the overall quality of life of epileptic patients.

Traditional epilepsy treatment relies conventional pharmacological interventions such as levetiracetam, phenobarbital, and lorazepam in addition to epilepsy-related surgery such as temporal lobotomy. Despite the existence of more than thirty AED medications licensed and approved by the FDA for long-term treatment of epilepsy, nearly 40% of patients never achieve seizure freedom.[15] Clinically diagnosed epileptic patients exposed only to conventional methods of treatment therefore run the risk of exposure to adverse effects as well as not obtaining remission. Further, adolescent patients tend to experience more frequent adverse effects that limit

[10] Prasad et. al. *Alternative Epilepsy Therapies: The Ketogenic Diet, Immunoglobulins, and Steroids*. S81-S95
[11] Vining et. al. *A Multicenter Study of the Efficacy of the Ketogenic Diet. 1433-1437*
[12] DiMario and Holland. *The ketogenic diet: A review of the experience at Connecticut Children's Medical Center.* 2002
[13]Kossoff et al. *Efficacy of the ketogenic diet for infantile spasms*. 2002
[14] Mady et al. *The ketogenic diet: Adolescents can do it, too*. 2003
[15] Hartmann et. al. *Use of Complementary and Alternative Medicine (CAM) by Parents in their Children and Adolescents with Epilepsy – Prevalence, Predictors and Parents' Assessment.* 11-19

their ability to work and participate in activities[reference], and can suffer from long-term side-effects of high-dose and/or AED polytherapy, leading to major cognitive and behavioral difficulties.[16]

Despite studies showing the negative impact that AED medications can have on behavioral and cognitive development of young adults, adolescents, and infants,[4,5,9,17,18] these drugs remain as the mainstay course of treatment within the United States. Behavioral problems can range from mild to extremely severe under the influence of AED medications. The practice of polytherapy, the use of the use of two or more drug combinations with different mechanisms of action can also influence on the expression and severity of behavior problems. Levetiracetam, an approved antiepileptic drug used for treatment in both children and adults, has been associated with caused behavioral problems including aggression and changed mood states such as depression, agitation, hostility, irritability and hyperexcitability.[19] Compared to nonusers, AED users have an increase in relative risk of death by 95%.[20] Heavy reliance on monotherapy and polytherapy use of AEDs has resulted in increased mortality. Charlotte Figi, a patient who is refractory to available conventional treatments, exemplifies the therapeutic success of seizure frequency reduction by use of alternative methods, hence warranting for more funding to resume needed research.

[16] Kwan, M.D., & Brodie, M.D. *Early Identification of Refractory Epilepsy*. 314-319
[17] Loring, D., *Cognitive Side Effects of Antiepileptics Drugs in Children.* Vol XXII. Issue 10
[18] Cross, J., *Neurodevelopmental effects of anti-Epileptic drugs.* 1-10
[19] G. K Mbizvo. *Levetiracetam add-on for drug-resistant focal epilepsy: an updated Cochrane Review.* 2012
[20] Tatyana S. et. al., *Antiepileptic drug use and mortality*. e2099-e2108

Born October 18th, 2006, Charlotte Figi came as a miracle healthy baby alongside her twin brother Chase Figi. At only the age of three months old, the life of baby Charlotte changed forever. Charlotte underwent her first seizure and, a week later, experienced another that lasted double the duration. Over the next few months, she frequently would have seizures lasting two to four hours and was hospitalized repeatedly. Medical tests accumulated up to nearly a million dollars. In the beginning, results displayed no signs of epilepsy and came back normal. Doctors were all stumped and could only discharge her.

As time progressed, the seizures continued, and the hospital stays grew longer. Charlotte was prescribed seven or more heavy-duty antiepileptic and addictive medications, displaying cognitive and neurological declines. At the age of nearly three years old, Colorado's Children's Hospital neurologist tested her for the SCN1A gene in a rare, yet severe condition known as Dravet Syndrome. A few months later, results showed the presence of a mutation in the SCN1A gene. By the age of five, Charlotte suffered as many as 300 grand mal seizures a week, lost the ability to walk, talk, eat, and would go into repeated cardiac arrest. Even with the use of AEDs, Charlotte Figi displayed no improvement. With more dedicated funding allocated towards research into alternative treatment methods, patients with similar cases to Charlotte can be assisted.

2. Review of the Literature

There is high reliance on the use of monotherapy AEDs as the mainstay of treatment, as mentioned in findings by Lia Santulli and Elisabeth Halma, although correlations of efficacy and

therapeutic success are disparate.[2122] In contrast, a review performed by Edward Maa, Robert Caraballo, and Norman Doidge delivers empirical data and testimonial stories to suggest that CAM therapies and the introduction of neuroplasticity to the field of Neurology also displays success in the overall reduction and treatment of epilepsy.[232425]

Advances in epilepsy treatment are occuring at a very rapid pace adding to the evolutionary field of medicine requiring practicioners, researchers, and healthcare providers to be at the forefront of acceptance to these changes. As healthcare providers struggle to keep up with current literatures and clinical work, inevitably, they often fail to exercise new trends and envision what the field of medicine could be in the near future.[9] The seven studies analyzed within this systematic review equally combat against this delimma and demonstrates experts who challenge the normative pressures of western medicine.

The issue of adverse effects is frequently underestimated, especially in children. Adverse effects in behavior and cognition, such as the previously mentioned, may lead to early discontinuation of AED medication treatment usage resulting in an increase in inadequate seizure control. Generally side effect severity is defined by an individual and not solely reliant on the clinician. Minimal side effects may be acceptable, with the result of good seizure control, whereas major side effects with or without seizure control are unacceptable.[7] This individual response can be interpreted inversely from one individual, or family, to the next. Seizure control

[21] Santulli et. al., *The Challenges of Treating Epilepsy with 25 Antiepileptic Drugs*. 211-219
[22] Halma et. al., *Behavioral Side-Effects of Levetiracetam in Children with Epilepsy: A Systematic Review*. 685-691
[23] Maa et. al., *The Case for Medical Marijuana in Epilepsy*. 55(6) 783-786
[24] Caraballo, et al., *Ketogenic Diet in Patients with Myoclonic-Astatic Epilepsy*. 151-155
[25] Doidge. *The Brain that Changes Itself: Stories of Personal Triumph from the Frontiers of Brain Science*. 2007
[9] Privitera M. *Epilepsy Treatment: A Futurist View*. 2017

in children who experience severe or refractory epileptic occurrences typically achieve improved control by using doses of AEDs that produce loss of function and abilities, therefore, delaying learning composition. R. E Appleton acknowledges, in many of these cases, a therapeutic compromise needs to be acquired whereby the major and head-injuring types of seizures are controlled without resulting in excessive sedation or loss of function.[7] With the lack relative studies, in many cases, this therapeutic compromise may be difficult to achieve. Impaired functionality and learning capabilities can be avoided using CAM methods.

This brief analysis will focus on some of the eight CAM therapies listed by Nicole Hartmann et al.[7], including non-conventional medical treatments, dietary approaches, herbal remedies, yoga, osteopathy, and homeopathic treatments. The evidence base for most non-conventional treatment options is generally limited and restricted to non-randomized and retrospective studies.

2.1 Ketogenic Diet

The effects of the ketogenic diet are similar to that of fasting in that the intake of high fat and low carbohydrate content promotes prolonged ketone production.[7] Before the development of AEDs for the treatment of epilepsy became popular and widespread, the ketogenic diet was the treatment of choice. In the 1990s, interest in ketogenic diets was reignited following prospective observational studies. Equally, intractable epilepsy and AED toxicity in children permitted the need for ketogenic diets as a less-invasive treatment.[7] There are risks associated with ketogenic diets including gastrointestinal upset, risk of dehydration and hypernatremia, kidney stones and vitamin deficiencies if not frequently monitored.[7] Despite these risks, children

treated with ketogenic diets showed improved cognition and behavior compared to adverse affects experienced from the use of AED's. This can result from direct effect of reducing seizure frequency but also indirectly via the reduction of AED use. [7]

2.2 Herbal Remedy (Homeopathy)

Cannabis sativa has a long history of medicinal use as treatment for a variety of whole-body ailments including rheumatism, pain, and convulsions. Before its dismissal following the Marijuana Tax Act of 1937 and classification as an illegal substance, cannabis sativa was available throughout the U.S. at all pharmacies for the prescription of multiple maladies.[23] Cannabis sativa consists of 489 known components, 70 of which are cannabinoids, while the remainder are neuroactive substances. Δ-9- tetrahydrocannabinol (THC) and cannabidiol (CBD) are two of the most common cannabinoids. Multiple randomized studies evaluating THC efficacy conducted within the period of 1970 to 1985 displayed protection in cats and prevention in baboons from kindled seizures with the use of Δ-9-THC. In addition, 93% of the sample population exhibited partial or full convulsion improvement with the administration of CBD.[21]

2.3 Yoga (Osteopathy)

Osteopathic medicine is a discipline with emphasis on the interrelated unity of all systems in the body, a whole person approach to medicine. This approach focuses to treat the entire person rather than a single symptom. Practitioners of osteopathic medicine help patients to cultivate mindsets and lifestyles that fight and prevent illness. Yoga, similar to osteopathic

[23] Maa et. al., *The Case for Medical Marijuana in Epilepsy*. 55(6) 783-786

medicine, promotes the body's natural tendency towards health and self-healing. Stress is known to be a leading factor for eliciting seizures and yoga aids by inducing relaxation.[7]

2.4 Epilepsy and CAM

Ketogenic diets were used as a CAM therapy in 90% of patients across the seven included studies (n=257). The remaining 10% was divided between osteopathic, homeopathic and CNB treatments. Epilepsy is a multidimensional condition that includes multiple aspects of the patient and can affect various parts of a persons cognitive, behavioral, social functionality. Nearly half of the epilepsy diagnosed population suffer from refractory seizures which can be defined by the International League Against Epilepsy (ILAE) as the persistence of seizures on three or more antiepileptic drugs in full doasage and total compliance over a period of 3 years.

Most patients report that epilepsy negatively impacts their social life due to the stigma associated with this condition, while others feel discriminated against in their work environments. Recently, compliance with AED medications has surfaced as a problem for patients diagnosed with chronic epilepsy, especially for those who require long-term and life-long therapy. To illustrate this, Hartmann et al. obtained approval from the Ethics Committee to conduct a structured interview process on patients aged 0 to 18 years with the diagnosis "epilepsy" by ICD-10-GM code which refers to inpatient and outpatient diagnosis of epilepsy. Of the 21 patients included in their use of CAM therapy study, 17 (81%) reported experiencing adverse side effects (ADE) of anticonvulsants. The ADE reports included the following answers: concentration deficit/fatigue, behavior problems/aggressiveness, delay in speech development, enuresis, diplopic images, liver impairment, dry skin, coryza, cold limbs, and weakening of

immune system[15]. These factors contribute to the reasons why medication compliance is an issue and why patients diagnosed with epilepsy may seek help from CAM.

The trend of using CAM for treating epilepsy does not differ from that in other medical conditions. Sirven et al.[26] conducted a study where 50% of patients cited the use of CAM therapies for non-seizure conditions, while 44% turned to CAM therapies specifically for seizure reduction. The use of alternative treatments is evidently not only useful for epilepsy but can also complement treatment of other medical conditions with less harmful adverse effects. In a study of 143 patients with focal or generalized seizures treated with ketogenic diets, Maydell and colleagues[27] found that approximately 48% of the patients demonstrated improved alertness, motor improvements, behavior improvements, sleep improvement and significant developmental progress with CAM therapy treatment. Additionally, the number and dosage of antiepileptic drugs required was reduced in relatively 50% of patients. Another study showed that amongst five children with epilepsy treated with CAM, primarily CNB, 100% had previously been treated with antiepileptic drugs.[27] AED medication use ranged from phenytoin, lamictal, and valproate with dosages of 150 to 625mg/day. Results showed that AED medication(s) were either reduced significantly or unchanged for all patients. During the period of treatment with CAM methods, each patient underwent a quality of life (QOL) follow-up providing testimonials to their use of ketogenic diets.[28] Testimony reports listed the ability to achieve academic adeptness, regain courage to drive again, become activists for children undergoing abuse, and decreased depression/anger.

[26] Sirven et al. *Complementary/alternative medicine for epilepsy in Arizona*. 576–577.
[27] Maydell et al. *Efficacy of the ketogenic diet in focal versus generalized seizures*. 2001
[28] Reiter and Andrews. *A neurobehavioral approach for treatment of complex partial epilepsy: efficacy*. 2000

In 2002, DiMario and Holland[12] reported similar testimonies and presented results comparable in outcome with other reports mentioned. Their research observed that 71% of their 18 patients experienced greated than 50% reduction in seizures, 17% of whom became seizure free within only the first 6 months of treatment. The etiology of children's epilepsy varied between idiopathic and symptomatic epilepsy. None of the improvements were statistically found to be related to patient age (P=0.97), sex (P=0.78), or epilepsy etiology (P=0.80)[12]. DiMario et al. conducted follow-up reports which showed that the number or dosage of antiepileptic drug per patient decreased signficantly, with more patients becoming AED free by the first 12 months.

Despite the limitations in sample population assayed, these studies suggest that there are a considerable number of patients affected by epilepsy who choose to try CAM therapies. All seven studies described in this analysis report data spanning a 12 - 24 month period of CAM method treatment. The Kossoff et al., [13] and Mady et. al.[14] retrospective studies were the only to report data about patient seizure improvement and reduction every 3 months. At the 12-month mark, 36 of the 43 (87%) patients treated with CAM methods showed > 90% seizure reduction. 20 of the 43 patients had a mean of 419 seizures per month (ranging between 2 - 3,000 seizures/month). A positive change in seizure frequency for patients experiencing nearly 3,000 seizures per month to greater than 90% reduction, by way of CAM methods is poignant. Such a tendency encourages us to look closer into the most popular CAM therapies and try to

[12] DiMario et al. 2002

understand their potential value. Ketogenic diets, CNB, and osteopathic/homeopathic therapies have proven themselves safe, and well-tolerated.

3. Problem Statement

3.1 Objective

This thesis systematically evaluated the therapeutic success of complementary and alternative medicine (CAM) methods as a treatment option for epileptic children. Of the multiple ways to define and monitor the impact of epilepsy on a patient's QOL, assessments where the patients can record their feelings on seizure severity and frequency are particularly useful to document and display progress following treatment changes. Data collected from patients and parents on the overall seizure control and effectiveness observed pre- and post- CAM therapy adoption was compared and tested for statistical significant differences It is critical to evaluate the effectiveness of CAM therapy treatment options as they can present tremendous improvements in behavioral and cognitive functionality.

3.2 Description of the Research Objective

The objective of this work was to determine the efficacy of CAM therapies on epilepsy by means of a meta-analysis. Various prospective studies have analyzed positive correlations between psychological health, therapeutic success, and physical health in epileptic patients. For the purpose of this study, due to limited data, the therapeutic success of CAM methods on pediatric patients ages 0-25 years diagnosed with epilepsy was the focus.

3.3 Research Questions

Non-pharmacological treatment of epilepsy can include surgery, diet alteration, body and mind stimulation, and other alternative therapies. This meta-analysis sought to answer the following questions: What can CAM therapies do for epileptic patients? What does statistical data display about the success rate in epileptic patients after adherence to CAM therapies? How do CAM therapies improve the patient's life and reduce epileptic occurrences?

4. Methodology

A meta-analysis is the statistical procedure for assessing previous research studies to derive conclusions on a particular research matter. Decisions regarding the utility and validity of a given hypothesis for an alternative therapy or intervention on epileptic patients cannot be based on the results from a single study. Results typically vary from one study to the next. By performing this type of quantitative study design, review of a large, and often complex and conflicting body of literature can be consolidated and examined. A Chi Square test is a statistical procedure used to examine the differences between categorical variables within the same population. Chi square testing in a meta-analysis report assumes that all the studies are measuring an identical effect and provides a p-value to test the hypothesis. Independent sample t-test are used to compare the means of two independent groups and determine if there is statistical evidence to indicate that the associated population means are significantly different.

Meta-analysis can be applied in a host of diverse fields. Pharmaceutical companies, combined with regulatory agencies, use meta-analysis to gain approval of drugs. Clinicians and multidisciplinary researchers in medicine, education, psychology, and beyond use meta-analysis to determine efficacy of interventions and compare them to determine which ones work best.

Meta-analyses can play a pivotal role for researchers as they aid in identification of questions that may be answered and those that remain un-answered. This analysis will provide evidence for the need of more research in Pediatric Neurology with focus in epilepsy. Additionally, it will identify which outcome measures are most likely to yield significant results, and the corresponding variants that are likely to be most powerful.

Statistical analyses were performed using the IBM SPSS Statistics 23. Multivariate analysis to study the relationship between sample population age, seizure reduction, and CAM usage was done using Chi-square test and independent t-test. Association between therapeutic success and CAM usage was analyzed using Chi-square test. Variables with $p < 0.05$ was considered statistically significant p value.

A meta-analysis study was conducted on 283 patients diagnosed with epilepsy to evaluate their therapeutic success (reduction in epilepsy occurrence) resulting from the use of CAM therapies. Observations were made on the same subjects over a 12+ month span and collected from seven studies. The sample size was determined by article selection and based on the subject participation with a duration period of 12 months or more. Epilepsy patients within the United States, who were under 25 years of age, experienced more than 5 epilepsy occurrences, and had been using a CAM therapy for at least 12 months were included. 388 subjects were excluded; 283 remained for evaluation. Although this study aimed to address the affect that CAM therapies can have on epileptic children's life, appreciation for allopathic "western and conventional" medicine is acknowledged.

When a treatment method is inconsistent from one study to the next, meta-analysis identifies common effects. The examination of variability or heterogeneity within inconsistent study data is a critical outcome. Different meta-analyses are essential tools used to summarize and categorize empirical evidence that fits pre-specified eligibility criteria to answer a specific research question accurately and reliably. This type of analysis helps healthcare practitioners, clinicians, and researchers keep up to date on healthcare initiatives; provide policy makers with crucial information to aid in judgement of risks, benefits, and harms of healthcare interventions. For the purpose of evaluating health care interventions, a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram was used (see Figure 1.). The flow diagram depicts the flow of studies through different phases of a systematic review. It thoroughly delineates records identified, included, and excluded, and the reasons for exclusion.

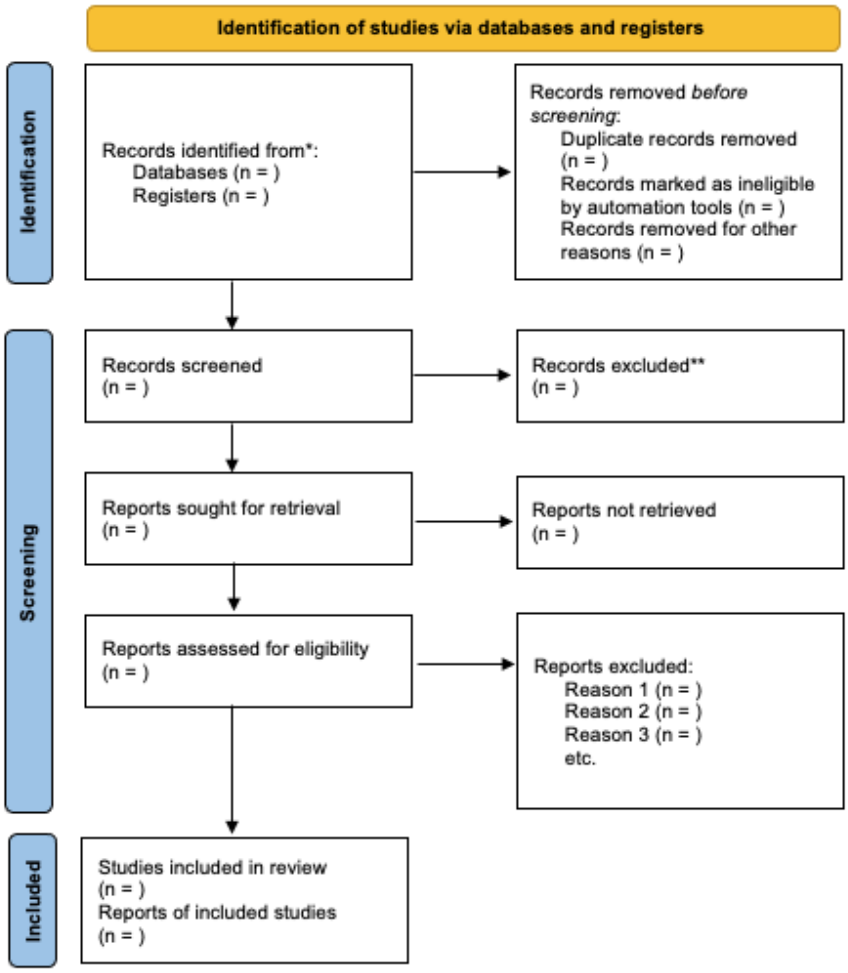


Figure 1. Prisma Transparent Reporting Of Systematic Reviews And Meta-Analyses

Articles were searched on the following search engines PubMed, EMBASE, NIH, Grants.gov, and Google Scholar. Primary articles involving CAM ketogenic diets, yoga, Ayurveda, botanicals, and EEG biofeedback were extracted, based on preliminary criteria such as year, geographic location, and the use of children under the age of 25, from the above-mentioned databases. A database of selected articles was created from an exhaustive search using serval interfaces assessing all medical literature pertaining to pediatric epilepsy use of non-pharmalogical treatment from 2000 to 2021. The term “epilepsy” was paired with the medical

subject key words “refractory epilepsy,” “neurologic condition,” and “seizures,” as well as the following terms: “focal seizures,” “children,” “adolescents,” “alternative methods,” and “CAM therapies.”

The inclusion criteria were as follows to answer the research questions: sample size, age, gender, course of disease, ICD-10 codes if applicable, and frequency of Epileptic seizures (Table 2). The data were based on content areas of study design, the type of CAM therapy performed, sample size, subject characteristics, and treatment duration. This meta-analysis did not involve the administration of a survey and in result did not need IRB approval. Covidence and Prism-P were used to aid in the managing of a systematic meta-analysis review. Once the combined articles were gathered based on the inclusion criteria, the above searches resulted in seven articles to be evaluated.

4.1 Covidence

A literature search and Covidence screening of forty articles found seven studies that met the inclusion criteria (Table 2) . This systematic meta-analysis review utilized Covidence to aid in the managing of a seamless review process and combine results, cacluate significance intervals (p value) and test heterogeneity of results, otherwise known as variability among studies.

Covidence is a web-based software platform that streamlines the production of systematic reviews. After importing each reference using the RIS text format, a title and abstract, and full text review screening was independently conducted to eliminate publications that fell outside the

inclusion criteria parameters. Covidence allows for the collaboration of multiple reviewers to screen and comment on imported studies and vote on if they should or should not be included in the data extraction process. This portion of data collection was completed without the aid of others, henceforth screened independently.

Table 2. *Inclusion and Exclusion criteria for a cross-sectional study of CAM methods on clinically diagnosed pediatric patients with Epilepsy: Covidence*

Inclusion criteria	**Exclusion criteria**
Patients < 25 years of age	Any acute or chronic condition that would limit the ability of the patient to participate in the study
Diagnosis of Epilepsy	Geographic location outside of the United States
Sample Size < 2000 patients	Use of AED medications, surgery, or western medical treatments for Epilepsy
Male and female participants	Adults > 25 years of age
ICD-10 Codes for Epilepsy Diagnosis	Refusal to give informed consent
Frequency of Epileptic episodes > 5	RTC studies > early 2000's

4.2 Article Selection for Meta-Analysis

Article selection was limited to primary research articles. Non-English articles, small sample size and geographic locations beyond the United States were excluded, as were articles focusing on only the use of AED treatments for epilepsy. Studies of adult patients, individuals older than 25 years of age, were also excluded. To be included, the article had to also have extractable data on patients who consistently used CAM therapies. That data must include the number of subjects, patients with sizable difference in the reduction of seizure frequency, age, patients with no change, and seizure type.

For the purposes of the meta-analysis, therapeutic success was defined as ≥ 50% of reduction of Epileptic episodes. This percentage was tallied after a cumulated 12 months of

monitoring. Conversely, patients experiencing < 50% seizure reduction after 12 months were considered to have displayed some but not full therapeutic benefit.

4.3 Meta-analysis of Diet, CNB & Homeopathy / Osteopathy Efficacy

Available empirical data fitting the inclusion criteria in Table 2 was analyzed to determine the overall efficacy of ketogenic diets, CNB, and homoeopathy / osteopathy methods. The following studies found in Table 3 reported the number of patients who continued to follow CAM therapy after a 12-month period vs. those who ceased therapy after an initial 3 months (referred to as discontinued). From the listed studies in Table 3, a meta-analysis was conducted to analyze the efficacy of keto diets, CNB, and homeopathy/osteopathy therapies on the overall therapeutic success in epileptic patients. The research synthesis process allowed for enhanced interpretation on whether the use of alternative medical treatment for epilepsy can result in improvement of seizure occurrence. A chi-squared test for the effect of heterogeneity, variability among studies, within the group of subjects who continued CAM therapy post 12-months was performed to denote if an intervention did or did not work similarly per patient or study. In doing so, one can determine the effect on each patient from the use of CAM therapies.

Table 3. *Included Studies: Measurement of Responses*							
Study	**Vining et al[29]**	**Maydell et al[26]**	**DiMario and Holland[12]**	**Kossoff et al[13]**	**Mady et al[14]**	**Reiter and Andrews[27]**	**Hartmann et al.[15]**
Study Type	Prospective	Retrospective	Retrospective 102 (43%): Discontinued	Retrospective	Retrospective	Retrospective	Prospective
Year	2002	2001	2002	2002	2003	2000	2016
Subject(s) (n)	135/237 102 (43%): Discontinued	68/143 75 (52%): Discontinued	18/48 30 (62.5%): Discontinued	23	20/45 7/20: NR 25 (55.56%): Discontinues	5/11 6 (54.5%): Disqualified	21/164 143 (87%): Non-CAM users
Type of Seizures	Intractable	Intractable	Idiopathic and Cryptogenic	Intractable	Intractable	CPS GTC	Cerebral Seizures
# of Seizures before Therapy	NR	NR	NR	NR	2-3,000/month	2-15/month	NR
# of Seizures after Therapy	NR	NR	NR	NR	2-3,000/month	<1/month	NR
Reduction (% after 12mo)	n=34; 100 n=37; ≥ 90 n=44; 50-90 n=20; <50	n=23; 100 n=15; ≥ 90 n=16; 50-90 n=14; <50	n=4; 100 n=7; 50-90 n=7; <50	n=3; 100 n=8; ≥ 90 n=12; 50-90	n=6; ≥ 90 n=7; 50-90	n=3; 100 n=2; ≥ 90	n=4; 100 n=6; 50-90 n=11; <50
Age / Age (yr.) Range	0.2 – 9.8	0.3 – 29.0	1.0 - 15.0	0.5 – 2.0	12.0 – 19.0	9.0 – 23.0	1.0 – 16.0
CAM Therapy	Keto Diet	Keto Diet	Keto Diet	Keto Diet	Keto Diet	Comprehensive Neurobehavioral treatment	Homeopathy & Osteopathy

CPS= Complex Partial Seizures, GTC=Generalized Tonic-Clonic, and NR= Not Reported

5. Data Analysis

First, Covidence and PRISMA flowchart were used to screen 40 articles fitting the inclusion and exclusion criteria. When screening articles, Covidence prompts reviewers with the following sections: "identification", "methods", "population", "interventions", and "outcomes".

[29] Vining et al. *Growth of children on the ketogenic diet*. 2002
[26] Maydell et al. *Efficacy of the ketogenic diet in focal versus generalized seizures*. 2001
[12] DiMario et al. 2002
[13] Kossoff et al. *Efficacy of the ketogenic diet for infantile spasms*. 2002
[14] Mady et al. *The ketogenic diet: Adolescents can do it, too*. 2003
[27] Reiter et al. 2002
[15] Hartmann et al. *Use of Complementary and Alternative Medicine (CAM)…* 11-19

Notes and in-depth commentary are made during this procedure. Second, after identifying records with useful data, information on the number of excluded articles, reasons for excluded articles, number of assessed articles and study demographics of the eligible studies was recorded (using PRISMA). This permitted the exporting of empirical data into .csv excel files to allow all notes from each study to be expressed in one sheet.

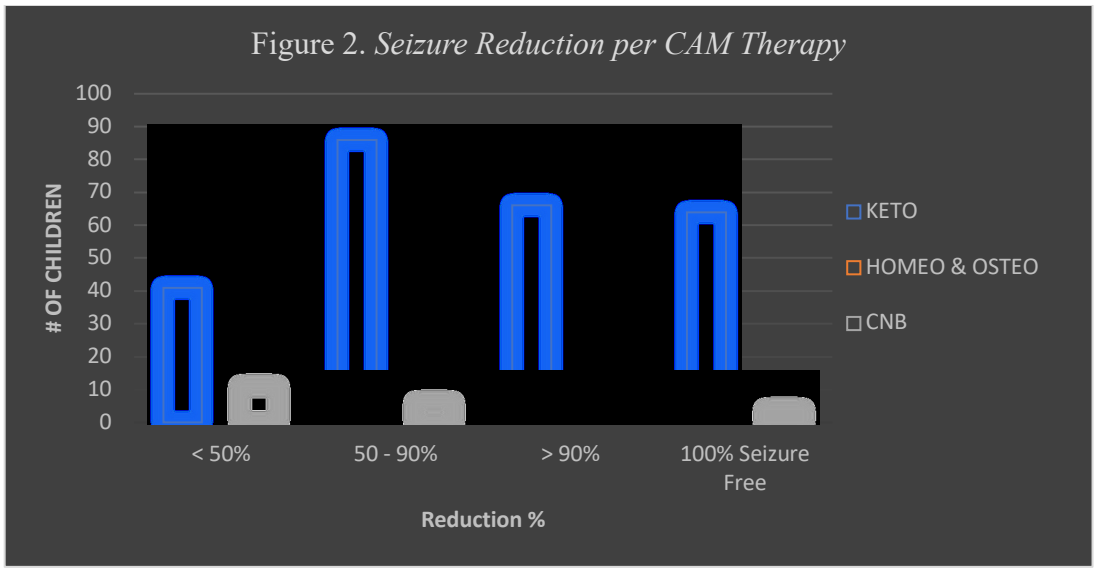
While screening studies, the type of CAM therapy implemented, population size, age variation, seizure reduction frequencies, and the number of children completing 12 months of therapy were documented. IBM SPSS Software was used to analyze data and survey for heteroscedasticity. The null hypothesis of this thesis was that CAM methods do not present improvement in therapeutic outcome for clinically diagnosed children with epilepsy. If the null hypothesis is to be rejected, the alternative hypothesis is accepted. The alternative hypothesis for this study states that CAM therapy shows enhanced therapeutic outcome for epilepsy in children. The statistical significance between the seven selected studies was assessed using p-value.

A *p-value* less than or equal to 0.05 indicates the statistical probability in which the test hypothesis should be rejected. The small p-value indicates evidence against the null hypothesis, as there is less than a 5% chance that the null is correct and therefore should be rejected. However, this does not mean that there is a 95% probability that the alternative hypothesis is true. A *p*-value greater than or equal to 0.05 is not statistically significant and indicates a higher probability to accept the null hypothesis. This means we retain the null hypothesis and reject the alternative hypothesis. The process of testing a hypothesis is fundamental to statistical inference.

A null hypothesis represents a theory that is put forward "either because it is believed to be true or because it is used as a basis for argument but has not yet been proved.

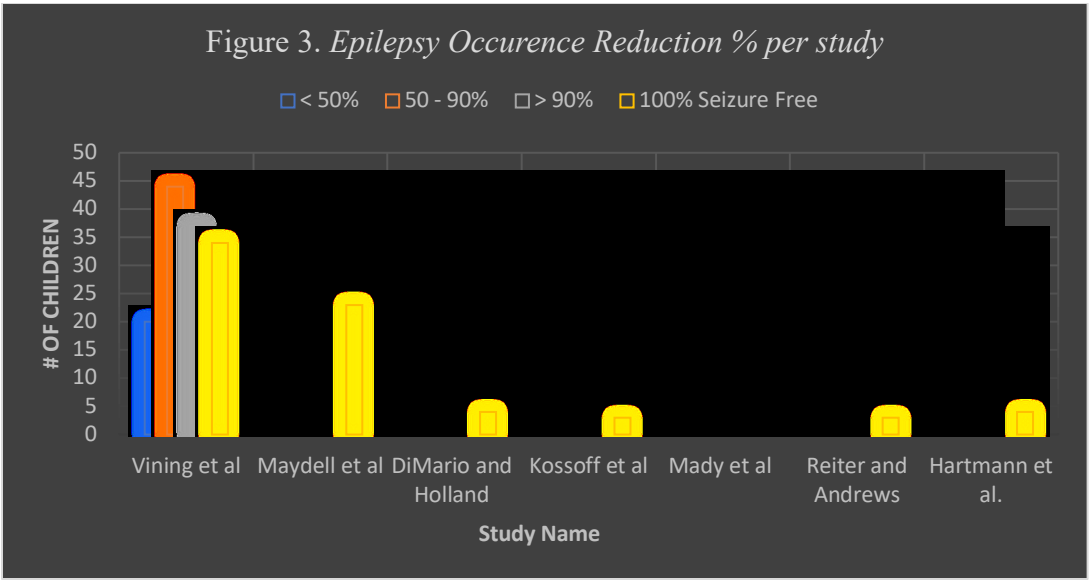
Empirical data results could aid in the conclusion of the testable hypothesis that complementary and alternative medicine therapies can successfully improve the overall quality of life for neurologic conditions such as epilepsy. In order to distinguish the therapeutic success in effectiveness of one CAM therapy compared to another, an independent t-test was performed. Independent t-tests provide levels of significance which refers to the likelihood that a random sample is or is not representative of a given population. A t-test resulting in a population displaying statistical significance from the choice of CAM therapy and percentage of therapeutic success suggests there is less than one in a hundred chance of being wrong.

A two-tailed t-test was executed on the collected studies [12-15,26-28] due to distinctive variabilities and sample sizes. The statistical power of the analysis is not as good because of limited data. Figure 2 exhibits the sum of children per CAM therapy (i.e., Keto, Homeo, & CNB) and seizure reduction percentage. Figure 2 depicts an easy visual of effectiveness per CAM therapy and sample size. This is important to display the lack of participants per CAM therapy which can affect any ultimate conclusions. While the data remains valuable, larger sample sizes would depict an even stronger result to draw conclusions from.



Varied populations shown in Figure 3 verifies the presence of heteroscedasticity, differences within a range of data. Heteroscedasticity is a statistical phrase that refers to the circumstance in which the variability of a variable is unequal across a range of values. With a limited quantity of studies addressing the efficacy of CAM therapy utilization for the treatment of pediatric epilepsy, populations become varied, random, and statistical power is slightly offset. The statistical power, often referred to as sensitivity, is how likely the study is to distinguish an actual affect from one of chance. A statistical power that is slightly offset occurs when limitations in data introduced, limitations including available study quantity. Despite these characteristics of the data, a comparison between the reduction of seizure occurrence from ketogenic diets to homeopathy/osteopathy treatments resulted in a statistically significant effect of p-value of 0.0062. In addition, a p-value of 0.0059 resulted from the comparison between ketogenic diets and CNB seizure reduction.

Figure 3. *Epilepsy Occurence Reduction % per study*



6. Discussion of Data Results

The therapeutic success of complementary and alternative medicine therapies on clinically diagnosed children with epilepsy is limited yet, very much desired for further research. With prevalent differences in variability and sample sizes per study, developing concrete conclusions can be more difficult, but still very attainable. This finding is consistent with previous research that determined there are not enough controlled studies demonstrating the efficacy of CAM therapies in the treatment of pediatric epilepsy.[30] Hurt and his colleagues conclude their study warranting more research in order to study the effects of CAM therapies on epileptic children at a larger capacity.

[30] Hurt et al., *Quantitative EEG neurofeedback for the treatment of pediatric...* 2014 (Hurt E, 2014)

6.2 Efficacy Over Time

Data from the seven studies were summarized to determine the efficacy of different CAM methods after 12 months (n=283). A large percentage of patients underwent the same treatment as displayed in Figure 4 with the breakdown of methods used within the included studies. Additionally, Figure 4 exemplifies clear evidence to why statistical power may not be as efficient due to the large sample size difference. Of the 238 patients, 137 (58%) were reported to have achieved complete seizure control and ≥ 90% seizure control, respectively (see Table 3 and Figure 4). (Note that the figure for ≥ 90% therapeutic success includes those with complete seizure control and does not include those who discontinued treatment.) This evidence proves that, despite limitations, CAM therapies can provide epileptic patients with hope, courage, strength, behavioral and cognitive control, and the ability to achieve flapping accolades in education. Statistical data exhibiting more than 50% of study participants with greater than 90% in seizure reduction, presents as avowed support for the alternative hypothesis.

Figure 4. *Methods of CAM used for Children with Epilepsy*

Used CAM Therapy (n = 283)	Treated children, n (%)
Keto Diet	257 (90)
Homeopathy	14 (5)
Osteopathy	12 (4.2)
Comprehensive Neurobehavioral Treatment	5 (2)
Naturopathy	4 (1.4)
Yoga	4 (1.4)
Vitamins	4 (1.4)
Kinesiology	2 (.7)
Chiropractic	2 (.7)
Others	7 (2.5)

7. Limitations

7.1 Limitations and Future Directions

There are limitations of the current study that should be considered, as well as considerations for future research. First, these data are representative of a cohort of young and school-aged children with inconsistent diagnoses and frequency of epilepsy. Second, article selection and screenings were all completed independently. Covidence allows for colleagues to work concurrently to screen articles and make notes as to reason of exclusion. Single screening, as opposed to group screening, can allow for substantial studies to be missed. Furthermore, statistical analysis conducted resulted from that of a heteroscedastic/unequal population. However, while findings from the current meta-analysis include subjects of infancy to the maximum age of 25 years old, it may not generalize to individuals with cognitive impairments and behavioral problems.

Findings from the current study may not generalize to adolescents and young adults with epilepsy or children with developmental disabilities. Future research should incorporate patients spanning a broader developmental level to determine if the modifiable factors identified in this study are relevant. Moreover, most patients with little to no autonomy over their treatment options are subjected to parent-reported decisions. A psychosocial factor from the child's perspective could be very critical for future research. This analysis only compared the effect of CAM therapies in chronic epilepsy on individual and family level influences and quality of life.

Other modifiable and nonmodifiable factors, including aspects of the health care system (e.g., access to resources, patient-provider communication) and community, should be examined in the context of pediatric epilepsy adherence. Many families lack knowledge on available

alternative means of treatment for neurological conditions and medical disciplines due to the lack of dedicated research in the field. Current publications on CAM therapies for neurologic conditions are highly funded throughout the EU, South America, Middle East, and North Africa but not North America.

Overall, there are a limited number of small studies, often with a lack of randomization, controls, and long-term follow-up. Many studies include statistical analyses to assess whether the observed changes were greater than chance alone, and few studies have directly compared different CAM therapy methods to each other. Methodologies were not consistent across trials (i.e., differing population ranges), making comparisons and the identification of best techniques come with a cavoite. While keto diets seem to carry a low risk of serious ad- verse events, side effects, which may include fatigue, feelings of detachment or fogginess, anxiety, headaches, insomnia, and irritability, have not been thoroughly studied.

Despite these limitations, results were quite similar across studies, showing beneficial effects in many patients. In general, however, there is insufficient evidence to make a recommendation regarding the role of CAM therapies in epilepsy. While keto diets, for instance, are FDA approved and backed by the American Academy of Neurology, there are no guidelines on other CAM therapy use. Homeopathy, osteopathy, acupuncture, EEG biofeedback, naturopathic treatment, yoga, kinesiology, vitamins and herbal remedies and neurofeedback may be used as an adjunct to standard treatments in interested patients, but with relatively little data to support efficacy.

8. Conclusion

Many uncertainties remain regarding alternative treatments for epilepsy, including the optimal cognitive or behavioral approaches, the ideal duration of treatment, the time course of potential improvement, and the types of patients who may benefit most. Evidence of the effectiveness of CAM therapy in gray literature[29,26,12,13] and anecdotal material similar to that of Charlotte Figi case study, led me to consider how benefits are supported in experimental studies. However, review of these studies demonstrate research gaps. We must consider funding and medical precedent to further investigate the benefits of CAM therapies in pediatric epileptic patients. Unfortunately, participation in such research may be limited by the need to travel for training or therapy, economic burden, unemployment, and many more unlike the ease of taking a pill. Nevertheless, CAM methods offer certain advantages. They tend to be less expensive, are non-invasive, lack serious side effects, require little technology, are more accessible, and maintain a great amount of seizure control.

In closing, reference to the previously addressed personal story of Charlotte Figi, will aid to bring this analysis to focus. Charlotte Figi's was diagnosed with epilepsy at 3 months, prescribed seven or more heavy-duty AEDs, and developed both cognitive and neurological impairment. Abnormal electroencephalography (EEG) readings displayed an occurrence of more than 300 episodes a week. Aside from those recurrent seizures, neurologic tests diagnosed her with a rare, yet severe condition known as Dravet Syndrome. Through an adjunctive therapy with a high concentration of cannabidiol (9)- tetrahydrocannabinol (CBD: THC), Charlotte's seizure frequency reduced from nearly 50 convulsive episodes a day to two or three nocturnal

convulsions per month.[22] Charlotte represents as a case study of the most severe epileptic complications which significantly improved with the use of an alternative treatment method. Empirical data on the use of adjunctive therapies like THC and CBD to gauge therapeutic success could not be gathered due to the lack of published studies.

Recently, healthcare professionals and scientific researchers have requested governmental funds and academic facilities to house their research on CAM therapies and Alternative/Osteopathic Medicine (i.e. Difficulties in Treatment and Management of Epilepsy…). Charlotte, a little girl who suffered from SCN1A-confirmed Dravet Syndrome, sparked a revolutionary change in healthcare as we know it for alternative means of medicine. For the purpose of continuing the revolutionary legacy of little Charlotte Figi, this meta-analysis was to conduct a research synthesis of studies that analyze the efficacy of CAM methods on the overall therapeutic success in epileptic patients. More research on the efficacy of CAM use for common neurological conditions is warranted.

[22] Maa et. al., *2014*

Appendix

Definition of Terms:

ICD-10 Code G40: A brain disorder characterized by episodes of abnormally increased neuronal discharge resulting in transient episodes of sensory or motor neurological dysfunction, or psychic dysfunction. These episodes may or may not be associated with loss of consciousness or convulsions.

CAM: Complementary and Alternative Medicine; a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine

AED: Antiepileptic Drugs; diverse group of pharmacological agents used in the treatment of epilepsy

ADE: Adverse Side Effects

Comprehensive Neurobehavioral CNB: A set of assessments and treatments addressing biological mechanisms of underlying behavioral disorders and psychological conditions

Polytherapy: means of overtreatment in epilepsy, excessive number or amount of AED(s) given resulting in suboptimal risk-to-benefit balance

Monotherapy: single drug treatment in epilepsy

Covidence: systematic meta-analysis review manager

Osteopathic Medicine: Medical discipline with emphasis on the interrelated unity of all systems in the body; a whole person approach to medicine.

Homeopathic Medicine: Medical discipline based on the belief that the body can cure itself

Refractory Seizures: The persistence of seizures on three or more antiepileptic drugs in full doasage and total compliance over a period of 3 years

Generalized Seizures: Abnormal electrical activity causing a seizure begins in both halves of the brain at the same time.

Focal Seizures/Complex Partial Seizures: A seizure occurs in just one area of the brain

Quality of Life: Greater than 50% reduction of Epileptic episodes. The standard of health, comfort, and happiness experienced by an individual

Heteroscedasticity: Statistical phrase that refers to the circumstance in which the variability of a variable is unequal across a range of values.

Heterogeneity: The quality or state of being diverse in character; variability among studies

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